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Abstracts

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O-145

In vivo effects of BQ-788 on ET_B receptor-mediated pressor and depressor responses

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We previously reported that the acute antihypertensive effects of mixed ET_A/ET_B antagonists were superior to those of ET_A -selective antagonists in hypertensive rats. In addition, it has been reported that BQ-788, an ET_B antagonist, reduces the efficacy of BQ-123, an ET_A antagonist, *in vivo*. To investigate the physiological effects of ET_B receptors on blood pressure, BQ-788 (3mg/kg/hr), BQ-123 (10mg/kg/hr) and J-104132, an ET_A/ET_B antagonist (3mg/kg/hr), were used. In Dahl salt-sensitive rats, BQ-123 alone decreased MAP by -13 mmHg, while BQ-788 alone increased MAP by +23mmHg. The maximal depressor effect of both compounds combined was similar to that of BQ-123 alone (-13 mmHg). However, the depressor effect of J-104132 (MAP: -25 mmHg) was greater than that of BQ-123 combined with BQ-788. BQ-788 completely inhibited the S6C-induced depressor response but did not affect the pressor response.In contrast, J-104132 completely inhibited S6C-induced depressor and pressor responses. These results suggest that, at least *in vivo*, the effects of BQ-788 as an ET_B antagonist should be interpreted more carefully because BQ-788 is more sensitive to the ET_B-mediated depressor response than to the pressor response .

O-146

Involvement of reduction of PAI-1 in beneficial effects of perindopril on prevention of stroke.

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Plasma plasminogen activator inhibitor-1 (PAI-1) would participate in coronary thrombotic process in patients with myocardial infarction. However, the role of PAI-1 in stroke has not been clarified. The present study was designed to examine whether plasma PAI-1 activity is enhanced in SHRSP with high salt loading. We also investigated whether PAI-1 activity is affected by treatments with anti-hypertensive drugs including perindopril. SHRSPs were continuously subjected to 1% NaCl intake and divided into seven groups (control, perindopril 2 mg/kg/day, propranolol 100 mg/kg/day, nicardipine 20 mg/kg/day, hydralazine 50 mg/kg/day, hydrochlorothiazide 100 mg/kg/day and losartan 50 mg/kg/day). Two weeks after treatments with these drugs, systolic blood pressure decreased in the group with hydralazine, nicardipine or perindopril. However, other three drugs did not affect blood pressure. Plasma PAI-1 activity in the control SHRSPs was significantly higher compared with that in WKYs, and it was lowered by losartan, hydralazine or perindopril. There was no correlation between plasma PAI-1 activity and blood pressure. These results suggest that PAI-1 contributes to the thrombotic process in stroke. In addition, the reducted of PAI-1 activity is not fully explained by hypotension alone. The beneficial effects of perindopril in stroke would be due to, at least in part, the reduction of PAI-1 activity.

O-147

Effect of long-term treatment with L-158809, a novel angiotensin II receptor (AT_1R) antagonist, on function of periaterial nerves in spontaneously hypertensive rats (SHR)

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We have reported that long-term treatment with AT_1R antagonist, candesartan, reduced vasoconstriction mediated by sympathetic adrenergic nerves. In the present study, the effect of long-term treatment of a novel AT_1R antagonists (L-158809) and angiotensin converting enzyme (ACE) inhibitor, temocapril, on the function of periaterial nerves was investigated in SHR. Male SHR (8-week-old) was received 0.001% and 0.005% L-158809 or 0.005% temocapril in drinking water for 8 weeks. At 16 weeks of age, blood pressure was measured and isolated mesenteric vascular bed was prepared for perfusion. Mean blood pressure in SHR was significantly lowered by the long-term treatment with L-158809 and temocapril. In the preparation treated by L-158809, periarterial nerve stimulation (PNS; 4, 8 and 12Hz) induced-vasoconstriction was significantly smaller than that in non-treated SHR. However, L-158809 and temocapril had no changes in release of norepinephrine (NE) by PNS. The vasoconstriction induced by bolus infusion of NE was significantly smaller than that in non-treated SHR. In preparation with active tone produced by guanethidine and methoxamine, PNS caused a frequency-dependent vasodilation mediated by CGRP nerves. Treatment with temocapril but not L-158809 (0.005%) increased the PNS-induced vasodilation. These results suggest that long-term treatment with L-158809 and temocapril reduces adrenergic vasoconstriction and temocapril enhances relaxation mediated by CGRP nerve.

O-148

Antihypertensive effects of endothelin (ET) and angiotensin II AT_1 receptor antagonists in several types of hypertensive rats

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The acute antihypertensive effects of J-104132, an ET_A/ET_B antagonist and losartan, an AT_1 antagonist, were characterized in several types of hypertensive rats. J-104132 did not affect blood pressure in normotensive rats (WKY and Dahl salt-resistant rats). Although J-104132 significantly decreased blood pressure in SHR and SHRSP, its antihypertensive effects were not as potent as those of losartan. In Dahl salt-sensitive rats and DOCA-salt rats, J-104132 markedly reduced blood pressure. In these models, losartan did not induce significant reductions in blood pressure. However, losartan had a remarkable antihypertensive effect in a renovascular hypertensive model (2-kidney, 1-clip); J-104132 had no depressor effect in this model. The antihypertensive actions of both J-104132 and losartan persisted until 24 hours after dosing in these models. These results suggest that ET receptor antagonists could be useful in the treatment of volume-dependent and/or salt-sensitive hypertensive patients who are insensitive to renin-angiotensin inhibitors.